Express Mail No. EV529813821US

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 May 2004 (27.05.2004)

PCT

(10) International Publication Number
WO 2004/043486 A1

(51) International Patent Classification[7]: A61K 38/55, 38/05, 9/00 // A61P 7/02

(21) International Application Number: PCT/SE2003/001738

(22) International Filing Date: 11 November 2003 (11.11.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0203349-6 12 November 2002 (12.11.2002) SE

(71) Applicant *(for all designated States except US)*: **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **EDMAN, Peter** [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). **WINGSTRAND, Karin** [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE).

(74) Agent: **GLOBAL INTELLECTUAL PROPERTY**; AstraZeneca AB, S-151 85 Södertälje (SE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/043486 A1

(54) Title: AN ACQUEOUS PHARMACEUTICAL FORMULATION COMPRISING THE THROMBIN INHIBITOR MELAGATRAN AND USE OF THE FORMULATION IN THE MANUFACTURE OF A MEDICAMENT FOR USE BY NASAL ADMINISTRATION IN TREATING THROMBOEMBOLISM

(57) Abstract: An aqueous pharmaceutical formulation comprising the thrombin inhibitor HOOC-CH_2-(R)-Cgl-Aze-Pab (melagatran), or a pharmaceutically-acceptable derivative thereof, a process for the preparation of such a pharmaceutical formulation, the use of such a formulation in the treatment of thromboembolism as well as a method of treating a patient in need of antithrombotic treatment and thromboembolism by using said formulation via nasal administration.

An aqueous pharmaceutical formulation comprising the thrombin inhibitor melagatran and use of the formulation in the manufacture of a medicament for use by nasal administration in treating thromboembolism .

The present invention relates to an aqueous pharmaceutical formulation comprising the thrombin inhibitor HOOC-CH_2-(R)-Cgl-Aze-Pab (hereinafter melagatran) or a pharmaceutically-acceptable derivative thereof, the use of such a formulation in the treatment of thromboembolism, as well as a method of treating a patient in need of such a treatment by using said formulation, via a particular route of administration.

Blood coagulation is the key process involved in both haemostasis (i.e. prevention of blood loss from a damaged vessel) and thrombosis (i.e. the pathological occlusion of a blood vessel by a blood clot). Coagulation is the result of a complex series of enzymatic reactions; one of the final steps is conversion of the proenzyme prothrombin to the active enzyme thrombin.

Thrombin plays a central role in coagulation. It activates platelets, it converts fibrinogen into fibrin monomers, which polymerize spontaneously into filaments, and it activates factor XIII, which in turn crosslinks the polymer to insoluble fibrin. Thrombin further activates factor V and factor VIII in a positive feedback reaction. Inhibitors of thrombin are therefore expected to be effective anticoagulants by inhibition of platelet activation, fibrin formation and fibrin stabilization. By inhibiting the positive feedback mechanism such inhibitors are expected to exert inhibition early in the chain of events leading to coagulation and thrombosis. Melagatran is a thrombin inhibitor in active development.

Peptidic or peptide like thrombin inhibitors, like many other peptide-like substances, are prone to limited absorption when administered. This may be due to the influence of different barriers of metabolic and physical character, such as enzymatic degradation, tendencies toward complex formation with components from the formulation or the biological environment, limitations in epithelial transport etc.

In seeking desirable absorption and a favourable pharmaco-kinetic profile for an active compound, many different administration routes are possible, such as oral, rectal, buccal, nasal, pulmonary, inhalation route etc., and are disclosed, for example in WO 96/16671 (US 5,795,896) which specifically concerns formulations of melagatran.

Additionally, it may be necessary to administer pharmaceutically active compounds frequently throughout the day in order to maintain a desired therapeutic level of active principle in plasma and/or body tissues. This is particularly the case where it is intended to deliver a uniform response over an extended period of time, and the most common routes

of administration used are oral and parenteral. However, the parenteral route can be inconvenient, and oral administration can result in unacceptably low bioavailabilities.

Nasal delivery is a feasible alternative to oral or parenteral administration for some drugs, although many factors may influence the permeability of nasal mucosa to different compounds and such administration is often less attractive. Potential advantages of nasal administration are high permeability of the nasal epithelium and, as a result of the rather large surface area of the nasal cavity and the relatively high blood flow, rapid absorption. Furthermore, self-medication is easy and convenient.

One object of the present invention is to provide pharmaceutical formulations comprising the thrombin inhibitor HOOC-CH_2-(R)-Cgl-Aze-Pab (melagatran), or a pharmaceutically-acceptable derivative thereof, which are suitable for administration via the nasal route, and which deliver attractive absorption characteristics and a favourable pharmaco-kinetic profile.

In order to achieve suitable absorption, many different formulations of this therapeutically active drug are possible. For example, WO 96/16671 discusses the use of absorption enhancing agents, such as, but not limited to, surface active agents, chelating agents, lipids, other drugs and polymers to obtain positive effects which result in an enhanced and/or less variable absorption of the therapeutically active agent.

We have studied the use of several absorption enhancing agents in nasal administration (see Experimental Section) which confirm the improved absorption disclosed in WO 96/16671.

However, despite these results, a limiting factor associated with the addition of enhancers to a formulation for nasal administration is the potential toxicity to the nasal mucosa. Nasal absorption enhancers are required to be non-irritating, non-toxic and non-allergenic or at least to have immediately reversible effects. Moreover, they should be potent, compatible with the drug and other excipients in the formulation and systemically inert in the concentrations used. Potential enhancers have to be carefully evaluated to be acceptable in their enhancing ability and overall safety profile, with regard to both local and systemic effects.

With these potential drawbacks in mind the development of nasal formulations would not appear attractive. This is particularly so for anticoagulant compounds such as melagatran, which might potentially lead to undesirable, or uncontrolled, bleeding in the sensitive nasal cavity.

However, as the results in the Experimental Section for healthy male humans demonstrate, it has now been found that the nasal administration of the therapeutically active thrombin inhibitor HOOC-CH_2-(R)-Cgl-Aze-Pab is particularly attractive in pharmaceutical formulations containing said therapeutically active compound, but without the use of additional absorption enhancers.

Accordingly, in one aspect of invention we provide an aqueous pharmaceutical formulation comprising the thrombin inhibitor HOOC-CH_2-(R)-Cgl-Aze-Pab (melagatran), or a pharmaceutically-acceptable derivative thereof, for use by nasal administration.

In another aspect we provide an aqueous pharmaceutical formulation comprising the thrombin inhibitor HOOC-CH_2-(R)-Cgl-Aze-Pab (melagatran), or a pharmaceutically-acceptable derivative thereof, for use by nasal administration in antithrombotic treatment.

In another aspect we provide an aqueous pharmaceutical formulation comprising the thrombin inhibitor HOOC-CH_2-(R)-Cgl-Aze-Pab (melagatran), or a pharmaceutically-acceptable derivative thereof, for use by nasal administration in treating thromboembolism.

Further aspects of the invention include :-

The use of an aqueous pharmaceutical formulation comprising the thrombin inhibitor HOOC-CH_2-(R)-Cgl-Aze-Pab (melagatran), or a pharmaceutically-acceptable derivative thereof, in the manufacture of a medicament for use by nasal administration in antithrombotic treatment.

The use of an aqueous pharmaceutical formulation comprising the thrombin inhibitor HOOC-CH_2-(R)-Cgl-Aze-Pab (melagatran), or a pharmaceutically-acceptable derivative thereof, in the manufacture of a medicament for use by nasal administration in treating thromboembolism.

A method of treating a patient in need of antithrombotic treatment by nasally administering an aqueous pharmaceutical formulation comprising the thrombin inhibitor HOOC-CH_2-(R)-Cgl-Aze-Pab (melagatran), or a pharmaceutically-acceptable derivative thereof.

A method of treating thromboembolism in a patient in need of such treatment by nasally administering an aqueous pharmaceutical formulation comprising the thrombin inhibitor HOOC-CH_2-(R)-Cgl-Aze-Pab (melagatran), or a pharmaceutically-acceptable derivative thereof.

An aqueous pharmaceutical formulation without a specific absorption enhancer present and comprising the thrombin inhibitor HOOC-CH_2-(R)-Cgl-Aze-Pab (melagatran),

or a pharmaceutically-acceptable derivative thereof, for use by nasal administration in treating thromboembolism, is provided by the invention.

An aqueous pharmaceutical formulation containing the thrombin inhibitor HOOC-CH_2-(R)-Cgl-Aze-Pab (melagatran), or a pharmaceutically-acceptable derivative thereof, and other ingredients conventionally used in pharmaceutical formulations (but not including additional absorption enhancer components) for use by nasal administration in treating thromboembolism, is provided by the invention.

An aqueous pharmaceutical formulation containing the thrombin inhibitor HOOC-CH_2-(R)-Cgl-Aze-Pab (melagatran), or a pharmaceutically-acceptable derivative thereof, for use by nasal administration in treating thromboembolism, is provided by the invention.

The aqueous pharmaceutical formulations described herein are for use with all aspects of the invention, for example, the use and method of treatment aspects.

A preferred pH range of the formulation is in the range pH 3 to pH 8, particularly pH 4 to pH 7, and most especially pH 4 to pH 6.

A preferred pH range of the formulation suitable for nasal administration (for example to avoid or reduce irritation) is pH 4.5 to pH 6.5.

The dosage form used is preferably an aqueous solution of melagatran, prepared by known techniques, usually in which the active substance will constitute between 0.1 and 99 % by weight of the preparation, more specifically between 0.1 and 50 % by weight, particularly between 0.5 and 40% by weight, and more particularly between 5 – 20% (for example 50 and 200 mg/ml).

A preferred dose range of melagatran is from 1mg to 9 mg melagatran in a volume for nasal administration of 5 – 400 µg/µL, more particularly 6 – 360 µg/µL, and most especially 25-150 µL.

A preferred patient for the nasal administration of the invention is a human patient.

The pharmaceutical formulations of the present invention comprising HOOC-CH_2-(R)Cgl-Aze-Pab, or a pharmaceutically-acceptable derivative thereof, are intended, primarily, for prophylaxis and treatment in arterial as well as venous thromboembolism. Other disease conditions in which thrombin inhibition is desirable are also provided for by the present invention, for example, inflammation and pulmonary fibrosis.

The term "inflammation" will be understood by those skilled in the art to include any condition characterised by a localised protective response elicited by injury or destruction of tissues resulting from any of the causes mentioned herein, and which is manifest by heat, swelling, pain, redness, dilation of blood vessels and/or increased blood

flow, invasion of the affected area by white blood cells, loss of function and/or any other symptoms known to be associated with the inflammatory condition. The term will thus be understood to include *inter alia* acute, chronic, ulcerative, specific, allergic and necrotic inflammation, as well as all other forms of inflammation known to those skilled in the art.

Melagatran, and derivatives thereof, may thus be used in the direct treatment of inflammation resulting from injury, from viral or bacterial infection, or from a disease characterised by inflammation as one of its symptoms. Such diseases include autoimmune diseases, such as rheumatoid arthritis, psoriasis, allergy, asthma, rhinitis, pancreatitis, uticaria and inflammatory bowel syndrome.

However, melagatran, and derivatives thereof, are preferably used in the treatment of inflammation in patients with, or at risk of, a disease in which inhibition of thrombin is desired or required (see, for example, those listed in international patent application WO 97/23499), such as a thrombotic disease. Although the treatment may be of patients whose inflammatory and thrombotic diseases are unrelated, we prefer that the treatment is of a patient with a thrombotic disease in which inflammation plays a part in triggering coagulation. For example, inflammation may arise in blood vessel walls due to the presence and/or the action of microbes and/or the agents released thereby, physical damage, atheroscelorotic lesions and other inflammation-inducing agents. It is preferred that melagatran, and derivatives thereof, are used in the treatment of inflammation in patients having, or at risk of having, a thrombus.

For the avoidance of doubt, as used herein, the term "treatment" includes the therapeutic and/or prophylactic treatment of inflammation.

The term "pulmonary fibrosis" (PF) will be understood by those skilled in the art to include any condition characterised by one or more of (a) collagen deposition in the lung, (b) scarring (fibrosis) of the lung (including the alveoli and in the interstitium), and/or (c) regions of severe thickening of the alveolar walls, one or more of which may result in a chronic stiffness in the lungs and/or a decreased ability of the lung tissue to transport oxygen.

The PF may be a secondary fibrosis, which may be brought on by an inflammatory condition, such as sarcoidosis, rheumatoid arthritis, systemic sclerosis, scleroderma, extrinsic allergic alveolitis, severe asthma, systemic granulomatosis vasculitis and/or adult respiratory distress syndrome (ARDS), or it may be "idiopathic" PF (IPF).

The term "IPF" will be understood to include any form of PF where the underlying causes of the condition are unknown and/or to include the definition provided in the

consensus statement in *Am. J. Respir. Crit. Care Med.*, 161, 646 (2000), the relevant disclosure in which document is hereby incorporated by reference.

Particular forms of IPF that may be mentioned include *inter alia* desquamative interstitial pneumonitis (DIP), acute interstitial pneumonia (AIP), non-specific interstitial pneumonia (NSIP), respiratory bronchiolitis-associated interstitial lung disease (RBILD), bronchiolitis obliterans organising pneumonia (BOOP), lymphoid interstitital pneumonia (LIP) and, particularly, usual interstitial pneumonitis (UIP) (see, for example, *Am. J. Respit. Crit. Care Med.*, 157, 1301 (1998)).

Also provided by the invention is a process for the manufacturing of a pharmaceutical formulation, for use according to the invention, comprising forming an aqueous solution of the therapeutically active compound HOOC-CH_2-(R)Cgl-Aze-Pab, or a pharmaceutically-acceptable derivative thereof, optionally adjusting the pH (optionally using a buffering agent) to a therapeutically acceptable pH and isotonicity, for instance between 3 to 8, preferably between 4 and 7 or 4 and 6, for example pH 5, and mixing all ingredients. The pH can be adjusted by adding e.g. HCl or NaOH.

The formulations of the present invention are free of additional absorption enhancer components, although other ingredients conventionally used in pharmaceutical formulations such as buffers such as K_2HPO_4 : Na_2HPO_4, carriers, thickening and precipitation agents and isotonic agents such as NaCl known by a skilled person in the art may also be added to a pharmaceutical formulation of the present invention. Pharmaceutically-acceptable solvents other than water may also be used if suitable for nasal administration.

"Pharmaceutically-acceptable derivatives" of melagatran includes salts (e.g. pharmaceutically-acceptable non-toxic organic or inorganic acid addition salts) and solvates. It will be appreciated that the term further includes derivatives that have, or provide for, the same biological function and/or activity as melagatran. Thus, for the purposes of this invention, the term also includes prodrugs of melagatran (such as ximelagatran). "Prodrugs" of melagatran include any composition of matter that, following administration, is metabolised *in vivo* to form melagatran in an experimentally-detectable amount, and within a predetermined time (e.g. within a dosing interval of between 6 and 24 hours (i.e. once to four times daily)). Formulations comprising pharmaceutically-acceptable derivatives of melagatran may be prepared for use within a pre-determined period of time, for example for immediate use, or for use within 2 to 6 hours.

Thrombin inhibitors other than melagatran, or a pharmaceutically-acceptable derivative thereof, may also be used in the invention.

The following description is illustrative, but not limiting, of aspects of the invention.

EXPERIMENTAL PART

Use of absorption enhancers

Using standard techniques, melagatran was administered to rats in formulations with and without the enhancers SDS (sodium dodecyl sulfate) or EDTA. The bioavailability was measured by analysis of blood plasma samples using standrad techniques.

The bioavailability of intranasal melagatran 20 µmol/ kg alone was approximately 10 %, with enhancers improving this result up to about 19%.

Nasal administration of melagatran in healthy male humans

The rate and extent of absorption of melagatran as well as the safety and tolerability were investigated after intranasal administration to six healthy male subjects (between 20 and 40 years of age, body weight between 66 and 86 kg). The trial comprised three study days, separated by wash-out periods of 6-28 days. On study day 1, a single dose of 5 mg of melagatran was administered. The following two study days 10 mg and 20 mg, respectively, were administered.

Samples for determination of plasma concentration of melagatran (by LC-MS) and for degree of anticoagulation were collected before and up to 10 hours after drug administration. Safety measurements included blood pressure, heart rate and recording of adverse events.

The absorption of melagatran after intranasal administration was rapid and the median bioavailabilities for the three dose levels, 5 mg, 10 mg and 20 mg, were 19%, 12% and 19%, respectively. The bioavailability of melagatran for the six subjects at the three doses ranged from 7% to 45%. There was no indication of a dose dependent rate or extent of absorption. The safety and tolerability of melagatran when administered nasally were considered satisfactory.

Preparation of melagatran test compositions

Melagatran was dissolved in water and the composition adjusted to a pharmaceutically-acceptable isotonicity and pH (such as pH 5). The solution was aseptically filled into a glass bottle and a pump and applicator fitted (to give a metered dose of 50 microlitres).

Melagatran liquid nasal spray 50 mg/ml, glass spray bottle containing 5 ml

INGREDIENT	FORMULA (mg/ml)
Melagatran	50
Hydrochloric acid for adjustment to pH 5	q.s.
Water purified	to 1 ml

Melagatran liquid nasal spray 200 mg/ml, glass spray bottle containing 5 ml

INGREDIENT	FORMULA (mg/ml)
Melagatran	200
Hydrochloric acid for adjustment to pH 5	q.s.
Water purified	to 1 ml

ABBREVIATIONS

Aze = (S)-Azetidine-2-carboxylic acid; Cgl = (S)-Cyclohexyl glycine; Pab = 1-Amidino-4-aminomethyl benzene.

CLAIMS

1. An aqueous pharmaceutical formulation comprising the thrombin inhibitor HOOC-CH_2-(R)-Cgl-Aze-Pab (melagatran), or a pharmaceutically-acceptable derivative thereof, for use by nasal administration.

2. An aqueous pharmaceutical formulation comprising the thrombin inhibitor HOOC-CH_2-(R)-Cgl-Aze-Pab (melagatran), or a pharmaceutically-acceptable derivative thereof, for use by nasal administration in antithrombotic treatment.

3. The use of an aqueous pharmaceutical formulation comprising the thrombin inhibitor HOOC-CH_2-(R)-Cgl-Aze-Pab (melagatran), or a pharmaceutically-acceptable derivative thereof, in the manufacture of a medicament for use by nasal administration in antithrombotic treatment.

4. The use of an aqueous pharmaceutical formulation comprising the thrombin inhibitor HOOC-CH_2-(R)-Cgl-Aze-Pab (melagatran), or a pharmaceutically-acceptable derivative thereof, in the manufacture of a medicament for use by nasal administration in treating thromboembolism.

5. A method of treating a patient in need of antithrombotic treatment by nasally administering an aqueous pharmaceutical formulation comprising the thrombin inhibitor HOOC-CH_2-(R)-Cgl-Aze-Pab (melagatran), or a pharmaceutically-acceptable derivative thereof.

6. A method of treating thromboembolism in a patient in need of such treatment by nasally administering an aqueous pharmaceutical formulation comprising the thrombin inhibitor HOOC-CH_2-(R)-Cgl-Aze-Pab (melagatran), or a pharmaceutically-acceptable derivative thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2003/001738

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 38/55, A61K 38/05, A61K 9/00 // A61P 7/02
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 0041716 A1 (AS-TRAZENECA AB), 20 July 2000 (20.07.2000), page 4, line 23 - page 5, line 2; page 5, line 4 - line 7, abstract --	1-6
X	WO 0195932 A1 (AS-TRAZENECA AB), 20 December 2001 (20.12.2001), page 11, line 9 - line 19, abstract --	1-6
A	US 5795896 A (JAN-ERIK LÖFROTH ET AL), 18 August 1998 (18.08.1998), column 2, line 1 - line 17, abstract --	1-6

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 January 2004	10 -02- 2004
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Malin Söderman/BS Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2003/001738

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9745138 A1 (ASTRA AKTIEBOLAG), 4 December 1997 (04.12.1997), page 3, line 21 - page 4, line 2 --	1-6
A	WO 0064470 A1 (AS-TRAZENECA AB), 2 November 2000 (02.11.2000), page 12, line 25 - page 13, line 5, abstract --	1-6
P,X	European Journal of Pharmaceutical Sciences, Volume 18, 2003, Cecilia Wadell et al, "Permeability of porcine nasal mucosa correlated with human nasal absorption", page 47 - page 53, abstract --	1-6

INTERNATIONAL SEARCH REPORT

Information on patent family members

24/12/2003

International application No.
PCT/SE 2003/001738

WO	0041716	A1	20/07/2000	AU	767077	B 30/10/2003
				AU	2336100	A 01/08/2000
				BR	0007452	A 16/10/2001
				CA	2356611	A 20/07/2000
				CN	1341028	T 20/03/2002
				EP	1051590	A,B 15/11/2000
				EP	1150704	A 07/11/2001
				IL	143985	D 00/00/0000
				JP	2002534477	T 15/10/2002
				NO	20013414	A 10/07/2001
				SE	9900070	D 00/00/0000
				US	6382554	B 07/05/2002
				ZA	200105275	A 26/09/2002
WO	0195932	A1	20/12/2001	AU	6449501	A 24/12/2001
				BR	0111546	A 15/04/2003
				CA	2410228	A 20/12/2001
				CN	1446101	T 01/10/2003
				EP	1294395	A 26/03/2003
				GB	0014134	D 00/00/0000
				NO	20025908	A 09/12/2002
				US	2003153506	A 14/08/2003
US	5795896	A	18/08/1998	AT	208628	T 15/11/2001
				AU	689994	B 09/04/1998
				AU	4191596	A 19/06/1996
				BR	9509853	A 30/12/1997
				CA	2206459	A 06/06/1996
				CN	1168635	A 24/12/1997
				CZ	9701470	A 18/02/1998
				DE	69523943	D,T 27/06/2002
				DK	799052	T 25/02/2002
				EE	3338	B 15/02/2001
				EP	0799052	A,B 08/10/1997
				SE	0799052	T3
				ES	2168395	T 16/06/2002
				FI	972332	A 02/06/1997
				HU	77655	A 28/07/1998
				HU	216631	B 28/07/1999
				IL	116153	A 30/11/1999
				JP	10513438	T 22/12/1998
				NO	972475	A 30/05/1997
				NZ	297118	A 23/12/1998
				PL	320692	A 27/10/1997
				PT	799052	T 31/05/2002
				SE	9404196	D 00/00/0000
				SK	61797	A 04/03/1998
				TR	960518	A 00/00/0000
				WO	9616671	A 06/06/1996
				ZA	9510242	A 03/06/1996
				SE	9501425	D 00/00/0000

INTERNATIONAL SEARCH REPORT

Information on patent family members

24/12/2003

International application No.
PCT/SE 2003/001738

WO	9745138	A1	04/12/1997	AU	722450	B 03/08/2000
				AU	3111597	A 05/01/1998
				CA	2253410	A 04/12/1997
				EP	1015022	A 05/07/2000
				ID	19472	A 00/00/0000
				JP	2000511526	T 05/09/2000
				NO	985558	A 27/11/1998
				NZ	332788	A 26/05/2000
				SE	9602145	D 00/00/0000
				ZA	9704386	A 01/12/1997
WO	0064470	A1	02/11/2000	AU	754405	B 14/11/2002
				AU	4633600	A 10/11/2000
				AU	5768499	A 14/03/2000
				BR	0009847	A 08/01/2002
				CA	2371008	A 02/11/2000
				CN	1356908	T 03/07/2002
				CZ	20013757	A 15/05/2002
				EE	200100543	A 17/02/2003
				EP	1112388	A 04/07/2001
				EP	1200118	A 02/05/2002
				HU	0200955	A 28/09/2002
				IL	145840	D 00/00/0000
				JP	2002542298	T 10/12/2002
				NO	20015107	A 19/10/2001
				SE	9901442	A 22/10/2000
				SK	14962001	A 04/06/2002
				TR	200103017	T 00/00/0000
				ZA	200108544	A 17/01/2003
				SE	9904419	D 00/00/0000

INTERNATIONAL SEARCH REPORT

International application No.
PCT SE2003/01738

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 5 and 6
because they relate to subject matter not required to be searched by this Authority, namely:

see extra sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Box II.1

Claims 5 and 6 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

Claim 13 relate to methods of treatment of the human or animal body by surgery or by therapy or diagnostic methods practiced on the human or animal body (Rule 39.1(iv)). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds or compositions